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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,343	04/11/2005	Jacques Mallet	BJS-3665-122	3751

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
06/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,343	MALLET ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36,43-49,51-53 and 58-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,36,43-49,51-53 and 58-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicant's amendment and response filed on November 26, 2008, to the non-final Office Action dated June 26, 2008, and the supplemental amendment dated March 11, 2009 have been entered. Claims 35, 53, and 58-67 have been amended, and claims 54 and 57 cancelled. Claims 68-71 were newly added. Accordingly, claims 35, 36, 43-49, 51-53 and 58-71 are pending in the Application and currently under examination.

Applicants state that the Notice of Non-Compliant Amendment dated March 4, 2009 was mailed in error and caused unnecessary delay, because the Examiner appreciated the intent of Applicants' claim amendments. Applicants further cite MPEP 714 G and MPEP 714.05/714.03 in support of their arguments. Applicants' arguments have been fully considered, but are not found persuasive.

It should be noted that MPEP 714 G is not directed to defective claim amendments, but rather inaccuracy in the paragraph number and/or page and line designated, or a lack of precision where the paragraph or section to which insertion of the amendment is directed occurs; Such is not relevant to the claim amendments dated November 26, 2008. MPEP 714.05 states: All amended applications forwarded to the examiner should be inspected at once to determine the following:… (C) If the amendment is fully responsive (MPEP § 714.03 and § 714.04) and complies with 37 CFR 1.121 >(MPEP § 714). The notice of non-compliant amendment dated March 4, 2009 clearly indicated that the amendments to claims 35 and 53 were not compliant with 37CFR § 1.121 (c)(2). Compliance with 37CFR § 1.121 (c) is not considered optional by the MPEP, and the Examiner was not in error regarding the nature of Applicants' claim amendments.

Response & Withdrawn Claim Objection

Claim 58 was objected to in the previous office action dated June 26, 2008, for failing to clearly distinguish or further limit the method steps of base claim 57. In view of Applicants'

cancellation of claim 57 and amendments to claim 58, obviating the grounds for objection, the objection is hereby withdrawn.

Response and Withdrawn Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 35, 36, 43-46, 54-58 and 64-67 were rejected in the previous office action dated June 26, 2008, under 35 U.S.C. §112, first paragraph, as not enabled for the full scope of the invention. Applicants' cancellation of claims 54 and 57 renders their rejection moot. In view of Applicants' amendment of claims to limit the claimed invention to *in vitro* or *ex vivo*, and plasmid or viral vectors, thereby obviating the grounds of rejection, the rejection is hereby withdrawn.

Response, Maintained & New Claim Rejections - 35 USC § 103

Applicants' claim amendments have necessitated the following new ground of rejection.

Claims 35, 36 and 46 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538). Claim 43 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538), and further in view of Ramezani et al. (Mol. Ther. 2:458-469; 2000). Claims 44, and 64-65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538) and Ramezani et al. (Mol. Ther. 2:458-469; 2000), and further in view of Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999). Claims 45-51, and 66-67 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view Paulding et al. (J. Biol. Chem. 274:2532-2538) and Ramezani et al. (Mol. Ther. 2:458-469; 2000), and Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999), and further in view of Aronov et al. (J. Mol. Nerurosci., 12:131-145; 1999). Claims 35, 52 and 59 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538) and further in view of Chang et al. (Curr. Gene Ther. 2:237-251; 2001). Applicants' cancellation of claims 54 and 57 renders their rejections moot.

The rejections set forth on pp. 6-8 of the office action dated November 14, 2006, pp. 4-6 of the Office Action dated August 3, 2007, and pp. 4-7 of the previous Office Action dated June 26, 2008 are maintained for claims 35, 36, 43-49, 51-53 and 58-67, and further applied to new claims 68-71 for reasons of record.

Claims 68, 69 is newly rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538) and Ramezani et al. (Mol. Ther. 2:458-469; 2000), and further in view of Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999), for reasons of record.

Claims 70 and 71 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538), Ramezani et al. (Mol. Ther. 2:458-469; 2000) and Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999), and further in view of Aronov et al. (J. Mol. Nerurosci., 12:131-145; 1999), for reasons of record.

The previous Office Actions summarized the teachings of Barry et al. as follows:

Barry et al. teach lentiviral vectors for provirus integration into nondividing mammalian cells, wherein the incorporation of two distinct posttranscriptional regulatory elements, namely a central polypurine tract (cPPT) and a human hepatitis virus posttranscriptional regulatory element (PRE) that provide increased transgene expression. Barry et al. further teach the use of CMV and RSV promoters in their vectors (Fig. 1; limitation of claim 47), to control the expression of the GFP marker gene (Abstract, limitation of claim 48). For viral vector production and virus packaging, plasmid constructs carrying the pRRL lentiviral vectors are co-transfected into human 293T cells with an HIV gag/pol packaging construct, hence the lentiviral vectors are replication defective (first column, p. 1105). Additionally, the foregoing transfection is plasmid mediated. Barry et al. also teach the virus mediated infection of HeLa cells *in vitro* for determination of lentivirus vector titers (second column, p. 1105). Further, transgene expression as determined by GFP expression was increased over the sum of the components alone, suggesting a synergistic effect (Abstract and Fig. 1). The lentiviral vectors of Barry et al.

additionally contain polyadenylation signals in their LTR regions (depicted by $(A)_n$ in Fig. 1, p. 1104), that constitute a third posttranscriptional regulatory element, well established to confer increased mRNA stability. It was previously indicated that as the instant specification does not define or limit the structure of a posttranscriptional regulatory element, the cPPT qualifies as a posttranscriptional regulatory element.

Applicants disagree and present arguments that appear to be substantially the same as those previously presented. Applicants cite *In re Albrecht*, that the unexpected synergistic effect is evidence of unobviousness. Applicants' arguments have been fully considered, but not found persuasive.

In response, it should be noted that synergistic effects of two posttranscriptional regulatory elements was specifically observed by Barry et al. as indicated above. Thus, synergistic effects of two posttranscriptional regulatory elements was an expected outcome. "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967).

Citing, the previously supplied Declaration under Rule 1.132, by Applicant Dr. Jacques Mallet, Applicants argue that he Central Polypurine Tract (cPPT) is not a posttranscriptional regulatory element; that is the "HIV DNA flap nuclear transporter" increases the vector transduction efficacy by about 10 fold, due to the stimulation of the genome vector nuclear import.

In response, it is again noted that while cPPT has been shown to increase nuclear transport and transduction efficiency, Barry et al. state that vectors encoding both the cPPT and post-transcriptional regulatory element provide enhanced transduction and transgene expression, than when present individually in a vector, further showing a 65-fold increase in EPO secretion when both PRE and cPPT were present (Title and Abstract). Therefore Barry et al. clearly describe synergy between the elements in increasing transgene posttranscriptional expression; and thus further identify the cPPT as a posttranscriptional regulatory element.

Applicants argue that the cPPT, even if considered to be a post transcriptional regulatory element, is not a post transcriptional regulatory element comprising a UTR region of a

eukaryotic mRNA. Such is not found persuasive, because the reference of Barry has not been applied for anticipation of the instant claims. The rejection is for obviousness over a combination of references. The deficiency in Barry is cured by the teachings of the secondary references. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). There is no requirement that Barry et al. alone disclose each and every claimed element.

It should therefore be noted that each of the claimed posttranscriptional regulatory elements comprising a UTR region and their respective functions was known in the prior art (as stated in the instant specification and admitted on the record by Applicants). That the combination of two posttranscriptional regulatory elements in a single vector encoding a transgene would synergistically increase transgene expression was taught by Barry et al. Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention by Applicants to combine any two of the known elements in a single vector, which amounts to simple substitution of one known element for another to yield predictable results.

Therefore, the rejections are maintained for claims 35, 36, 43-49, 51-3 and 58-67, and further applied to new claims 68-71 for reasons of record and the foregoing discussion.

Conclusion

Claims 35, 36, 43-49, 51-53 and 58-71 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633